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MANAGEMENT OF PERIPHERAL EDEMA, INCLUDING LYMPHEDEMA OF THE ARM AFTER RADICAL MASTECTOMY

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INCAPACITATING, intractable edema of the extremities has long been a difficult problem to manage. Surgical attempts to create new lymphatic channels by means of subcutaneous tubes, strings, or pedicled skin grafts have not been consistently successful. In recent years, encouraging results have been achieved with technically improved methods of correcting, when possible, the underlying causes of vascular obstruction or insufficiency, reducing the weight of the obese patient, and selectively using diuretics and various forms of elastic or other compressive supports.

The purpose of this report is to describe a program of management that has been successful in 26 consecutive patients with edema of the arm, and in 83 consecutive patients with edema of the leg. Treatment is based upon the principle of squeezing edema fluid from the extremity by gentle, controlled pneumatic massage, then measuring and precisely fitting the extremity with a prestressed, elastic sheath.* The function of the sheath is to maintain interstitial pressure that favors continuous capillary absorption of the edema fluid. The special advantage of the elastic sleeves and stockings used in this study, over the commercial products in standard sizes, is in the precise individual fitting of the extremity.

Considerations in Treatment—The Upper Extremity

The incidence (up to 30 per cent) of edema of the arm following radical mastectomy attests to the fact that this is a common and serious complication.

Treatment was performed by Miss Gertrude B. Rose and Mrs. Robert D. Kruse of the Department of Physical Medicine and Rehabilitation.

The extensive removal of axillary lymphatic channels and the stripping of the adventitia of the axillary vein leave only a few lymphatic channels[1] to function, and these are exceedingly vulnerable to obstruction by infection. Probably infection is the most common cause of the ensuing lymphedema; less common causes are occult recurrent neoplasm, occlusion of the axillary vein, and radiation fibrosis. Excessive lymphedema of the arm has been controlled effectively with various types of massage and elastic support.[2] However, there has been little success in preventing recurrent cellulitis, induration, and acute swelling of the arm, using exercises, ultrasound, numerous operative approaches to establish new lymphatic channels, and radiotherapy to the arm itself.

Halsted[3] termed the lymphedema, "elephantiasis chirurgica," and observed it less often after he modified the technic of wound closure so as to reduce necrosis of the edge of the wound, and fluid collection beneath flaps. He believed that infection was largely responsible for postoperative lymphedema of the arm, and cited the conclusions of Matas: "The one etiologic factor which seems to be inseparable and essential to its pathogeny is infection—frequently repeated—which brings about permanent alterations in the vasculolymphatic apparatus of the skin and its underlying connective tissue."

The onset of lymphedema months or years after operation, particularly in patients whose wounds healed primarily without necrosis, infection, or fluid collection, has been poorly understood and continues under investigation. In the present study, a careful record was made of all postoperative infection, even when it was trivial. Physical evidence of infection ranged from overt cellulitis with fever, pain, and hard, brawny edema, to the faintest suggestion of induration and warmth in the posterior upper arm. Because in one patient without clinical evidence of infection a severe cellulitis developed after treatment with pneumatic massage, all patients with lymphedema of the arm were treated prophylactically with an antibiotic prior to massage.

Materials and Methods

The types of clinical edema encountered in this study are summarized in *Tables 1* and *2*. The duration of edema of the arm before treatment was as follows: two months (one patient), nine months (two patients), one year (one patient), one and one-half years (four patients), two years (six patients), three years (three patients), 3½, 5, 6, 7, 7½, 9, 10, 17, 19 years (one patient each). In three patients with active infection, cultures of tissue fluid aspirated from the posterior upper arm yielded coagulase-positive and pencillin-resistant *Staphyloccus aureus.*

Management of lymphedema of the arm consisted of the following five phases. *Phase 1.—Careful instruction in care of the hand and arm to prevent even trivial superinfection.* Essential features included protection of the hand and arm from needle and pin puncture wounds, detergents, hangnails, burns, and neglected minor infections. *Phase 2.—Administration of an antibiotic to control possible infection whether*

Table 1.—*Analysis of factors in patients with edema of the arm after radical mastectomy*

Number of patients							
Total	Wound drained	Fluid under flaps postop.	Postop. roentgen therapy	Clinical evidence of infection before therapy	Onset of lymphedema: Early	Onset of lymphedema: After 3 months	Obvious response to antibiotic*
26	11	16	20	17	10	16	17

**All patients were treated with erythromycin. Three patients were also treated with Albamycin (novobiocin sodium), The Upjohn Co. One patient was also treated with Albamycin (novobiocin sodium), Upjohn; and Kantrex (desoxystreptomycin), Bristol Laboratories, Inc.*

Table 2.—*Analysis of factors in patients with edema of the leg*

Etiology of edema	Number of patients	Duration of edema, yr.	No. of patients with: Ulcers of the leg	No. of patients with: Recurrent infection
Venous insufficiency; stasis syndrome, varicose veins	46	1 to 21	21	7
Postphlebitic	20	1/12 to 20	8	7
Obstructive edema				
Pelvic cancer	11	1/12 to 2	0	0
Vena cava occlusion	2	2 to 14	0	0
Lymphedema praecox	4	10 to 23	0	4

or not it was clinically evident. In 17 of 26 of the patients, infection was clinically evident, in most in the form of erythema, heat, and hard, brawny induration of the arm and forearm; in others, infection was subtle and appeared only as a strip of warmth and induration of the posterior upper arm. The initial course of antibiotic consisted of 250 mg. of erythromycin, four times daily, for a period of one

week, or until all clinical signs of infection disappeared. More recently, the problem of drug-resistant staphylococci has required the judicious use of the new anti-staphylococcal drugs. *Phase 3.—Application of intermittent pneumatic massage of the extremity (Fig. 1).* This treatment was deferred until all evidence of infection had

Fig. 1. The technic of pneumatic massage of the arm; the patient may be treated either in the sitting or in the supine position.

disappeared. Massage was continued for multiple three-hour periods until no pitting edema of the arm remained. *Phase 4.—Measurement for a precisely fitted elasticized nylon sleeve (Figs. 2-4).* When edema extended to the dorsum of the hand, the sleeve length included a gauntlet extension. *Phase 5.—Postural rehabilitation by means of trapezius exercises.* Exercises were taught to correct the slumped posture assumed by many women because of the great weight of the swollen arm. Several of the patients also had an "outlet syndrome" on the involved side, which responded well to improved posture and exercises.

The Lower Extremity

Patients with edema secondary to incompetent varicose veins, postphlebitic syndrome, occlusion of the inferior vena cava, or obstructing pelvic neoplasm were treated with pneumatic massage until all edema had disappeared from the

Fig. 2. Method of measuring the extremity with paper tapes for precise fitting of a prestressed elasticized nylon or dacron sheath.

Fig. 3. Standard arm sheath that extends from the wrist to just below the deltoid insertion.

Fig. 4. Arm sheath with gauntlet extension to the base of the fingers, for patients with edema of the dorsum of the hand. Moleskin is inserted at the antecubital fossa to prevent chafing.

leg, and then were fitted with long or short, or long and short stockings *(Figs. 5 and 6)*. Ulcers of the leg were first encouraged to heal by means of continuous elastic support. Patients with chronic refractory ulcers were admitted to the hospital for excision and skin graft of the ulcer area in conjunction with appropriate venous surgery prior to being fitted for stockings. Patients who had edema of the legs and acute infection were hospitalized and treated with elevation of the legs, and systemic antibiotics prior to being fitted for stockings.

The four patients with lymphedema praecox were treated as outlined above. One patient received additional therapy: the entire lower leg was infiltrated with procaine hydrochloride and hyaluronidase prior to pneumatic massage. The injections were not greatly beneficial, presumably because of the nature of the lymphedema and its long duration.

Materials and Technic

Several varieties of pneumatic pumps and sheaths were tried, the goal being an automatic cycling pump with controllable degree and duration of pressure cycles, comfortable to the patient, and practical for inpatient or for outpatient use. It was learned that a milking type of massage with pressure gradients beginning peripherally and progressing proximally, is not essential. Elevation of the

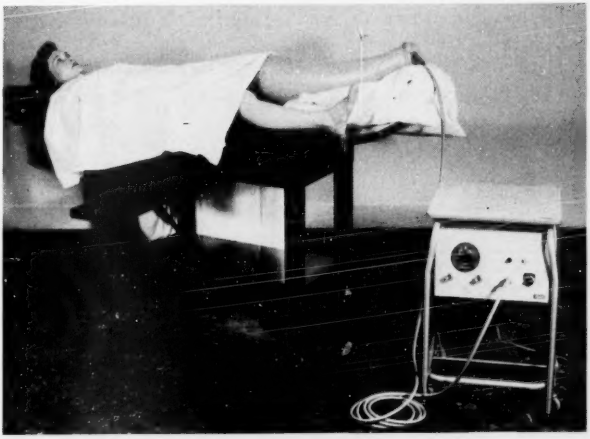

Fig. 5. The technic of pneumatic massage of the leg; both legs may be treated simultaneously.

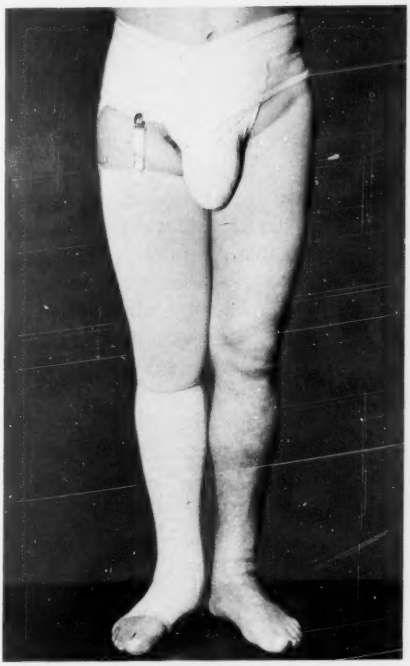

Fig. 6. Long and short stockings showing support suitable for male patients.

extremity, and an evenly distributed increase in interstitial pressure is sufficient, together with rhythmic release of the pressure for the comfort of the patient. This was accomplished by a tubular plastic bag* into which the stockinette-clad extremity was placed for from two to 12 hours. The most efficient pump used had three channels for simultaneous treatment of three patients, with pressure and exhaust phases adjustable reciprocally as fractions of a three-minute cycle. The pump generated pressures as high as 150 mm. of Hg; maximal pressures of 75 mm. of Hg were used on the arms, and from 125 to 150 mm. of Hg on the legs.

The primary purpose of pneumatic massage was to permit the fitting of an elastic sheath over an infection-free limb rid of excessive fluid. The limbs were measured by means of individual paper tapes. The material of the sleeves or stockings was of sufficient weight to provide good support with maximal comfort, but, because of its relative thinness, sleeves had to be replaced about every four months and stockings about every three months. Patients with massive edema of the legs sometimes required both long and short stockings; some type of suspension support was necessary to keep the long stockings drawn smoothly without wrinkles. The cost of the appliances was considered to be reasonable by the majority of patients.

Results

The upper extremity. The results of treatment of lymphedema of the arm after radical mastectomy were gratifying. Reductions in the size of the arms ranged from return to normal, to disappearance of only pitting subcutaneous edema. A long history of recurrent cellulitis was more prejudicial to an excellent response than was a long duration of edema. This might be expected because of fibrotic changes in the skin and subcutaneous tissues after chronic or recurrent infection. Patients have been enthusiastic about the results, apparently because physically the arm became much lighter and more comfortable, and the range of motion at elbow, wrists, and fingers increased; and psychologically, a positive, aggressive program of treatment was welcome after months or years of their being told that nothing could be done to help the disability. Failure of treatment was largely due to the psychologic reluctance of certain patients to accept any disability, or the knowledge that their arms could never be rendered completely normal. Those patients refused to wear the elastic sleeves, expressed disappointment in the entire program, and were the only patients who have had recurrent bouts of infection.

The lower extremity. Continuous control of edema without recurrent ulcers or recurrent cellulitis occurred in 79 of the 83 patients treated. The four failures were due to physical inability to put on the snug stockings, in two instances, and refusal by two obese patients to adhere to reducing diets and to wear foundations to support their long stockings. The four patients with lymphedema praecox were of special interest: in only one of them dramatic reduction in the size of the

**Pneumatic sleeves and pumps were supplied by the Jobst Institute, Toledo, Ohio.*

leg was obtained, but all have continued to use the elastic supports and none has had recurrence of infection.

Comments

The results in most patients have been encouragingly good. Pneumatic massage has been repeated periodically at the request of some patients who have allowed edema to recur because they failed to replace worn-out appliances early enough. Enthusiasm of patients regarding control of excessive edema and recurrent infection has been proportional to the original amount of edema and disability. The most dramatic response to treatment was obtained in a woman referred for amputation of both legs because of intolerable pain associated with a severe postphlebitic syndrome: after treatment and the wearing of both long and short stockings on each leg, she has been free of edema, pain, and progressive stasis changes, and has had normal use of the legs for the past six months.

Adjunctive use of weight-reducing diets, diuretics, and local foot care has been individualized. Diuretics have proved useful and safe when taken every other day during the week before menses in younger women.

Summary

A program for individualized therapy of edema of the extremities and its complications is described. The importance of infection in etiology and treatment of lymphedema of the arm following radical mastectomy is stressed.

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NONCHROMAFFIN PARAGANGLIOMA OF THE GLOMUS JUGULARE

Review of the Literature and Report of Six Cases

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THE uncommon neoplasm of the temporal bone known as the "glomus jugulare tumor," "chemodectoma" or "non-chromaffin paraganglioma" of the glomus jugulare has been widely discussed in medical literature since the true nature of this neoplasm was recognized by Rosenwasser.[1]

The prior recognition that nonchromaffin paraganglionic structures existed in the region of the temporal branch of the jugular bulb is credited to Guild.[2,3] Zettergren and Lindström[4] confirmed the observation of Guild,[3] who described the glomus jugulare as being composed of one or more "jugular bodies," the average number being about three per ear. He stated that the sites of more than half of these jugular bodies are the adventitia of the dome of the jugular bulb and the portion of Jacobson's or Arnold's nerves in the jugular fossa. In one fourth of the patients, glomic bodies were in the mucosa of the cochlear promontory in association with the tympanic plexus of Jacobson's nerve. In one fifth of the patients, jugular bodies were in the tympanic canaliculus, and in other patients they were in the descending facial canal.

The normal histologic appearance of the glomus jugulare is generally considered to be similar to that of the carotid body.[2, 3, 5] Guild[2, 3] found that using material from the temporal bone impeded the study of the cytologic details because extensive decalcification first was necessary. He described the structure as an aggregate of capillary or precapillary sized blood vessels arranged in coils or loops about nests of epithelioid cells; venules, in contrast, were straight. A fibrous capsule surrounded the entire structure, and fibrous septa continuous with the capsules were in the larger glomera. Furthermore, he noted variation in the proportion of epithelioid and vascular elements in the several glomera in one patient. In some glomera the epithelioid cells predominated; whereas, in others the vascular elements were most prominent. However, within a given ear with more than one glomic structure the histologic appearances of the glomera were likely to be the same. Nonmedullated nerve fibres supplied the glomic structure and were between the epithelioid cells. The size of the nerve entering the structure was unusually large for the size of the structure innervated, but the type of nerve ending was indeterminate. The chromaffin reaction of the epithelioid cells was negative.

Huppler, McBean, and Parkhill[6] may have disclosed a physiologic function of the glomus jugulare. Their provocative case supports the assumption that the behavior of the glomus jugulare is similar to that of the better-known members of the nonchromaffin paraganglia, the carotid and aortic bodies. The patient had

episodes of dizziness and "blacking out" initiated by coughing, sneezing, yawning, and breathing deeply in succession several times. They point out that at high altitudes the normal person constantly overbreathes and thus decreases his carbon dioxide tension and buffer base. The patient with the apparently functioning tumor chronically had to overbreathe; as a consequence he was subject to symptoms of hyperventilation—the "blacking-out" episodes.

The similarity of structure, innervation, and neoplasms of the glomus jugulare to those of other nonchromaffin paraganglionic members of the chemoreceptor system, i.e., carotid and aortic bodies, paraganglion intravagale or juxtavagale, and paraganglion ciliare, warrants inclusion of the jugular bodies in this system.[7-11] The embryogenesis, physiologic functions, and histologic features of the carotid and the aortic bodies have been well delineated,[12-32] and just as these structures arise in close association with the cranial nerves and branchial arches so apparently does the glomus jugulare. Histologically there appear to be no significant differences among other members of the chemoreceptor system. The rare, functioning neoplasms of the glomus jugulare tend to confirm similar physiologic functions.

Tumors of the glomus jugulare have been recognized in six patients at the Cleveland Clinic, two of whom eventually died, and were studied at necropsy. These patients had most of the clinical and pathologic features characteristic of these neoplasms.

Case Reports

Case 1. A 28-year-old white woman was first examined here in March, 1940, because of ataxic gait, and mild vertigo. About three years previously (July, 1937) she noted the onset of an imminent dysphasia associated with loss of fluids through the nose, and the sensation of obstruction at the cricoid level; this condition became severe when she was tired or nervous. About January, 1939, she began to have persistent hoarseness. Six months later (June, 1939) she commenced to have frequent nausea and vomiting, and deafness in the left ear. Apparently intermittent tinnitus had been present since 1937. At no time did she have headaches.

Otolaryngologic examination disclosed a red and thickened area in the posterior portion of the left tympanic membrane, which had the gross appearance of granulation tissue. There was severe loss of hearing in the left ear. The left vocal cord was in the cadaveric position and did not move during phonation. Neurologic examination disclosed nystagmus on lateral gaze bilaterally. The left corneal reflex was absent, but no extraocular palsies were noted. The left side of the tongue was atrophic and upon protrusion was deflected to the left. There was paralysis of the left side of the palate and pharynx with anesthesia of the left posterior pharyngeal wall. The left sternocleidomastoid and rhomboid muscles were atrophied and weak. The abdominal reflexes were absent. The gait was unsteady and the Romberg's sign was present as evidenced by a slight swaying. Roentgen examination of the skull showed inconclusive evidence of changes in the mastoid area, and no abnormalities of the petrous bones.

The patient was admitted to the hospital and an aspiration biopsy of the left middle

ear was attempted. One week later a suboccipital craniectomy was performed. At operation a soft, gray-and-reddish irregular mass of tissue was observed along the left side of the medulla. The surgeon palpated a loss of part of the left petrous bone. Neoplastic tissue appeared to have grown through the occipital bone to involve the overlying muscles. A biopsy specimen was taken and the pathologic diagnosis was hemangioendothelioma. A subsequent review reclassified this neoplasm as a non-chromaffin paraganglioma of the glomus jugulare.

After the operation the patient was given irradiation therapy of 5,550 r to the neoplastic area. The neurologic defects remained substantially the same, though the gait, swallowing, and phonation improved. She had experienced no increase in severity of symptoms when last seen in 1948.

Case 2. A 48-year-old white woman was first examined here in September, 1950, because of almost total loss of hearing. Six years previously (1944) a mass and tinnitus developed in the right ear. A biopsy specimen was studied in 1945 and was reported to be a hemangioma. Following the biopsy there was considerable foul-smelling purulent discharge from the external auditory canal. The patient was given irradiation therapy; the size of the aural mass decreased considerably. During the next five years loss of hearing in the right ear increased notably, and by 1950 it was almost complete.

Physical examination here disclosed a large polypoid tumor that filled the right external auditory canal. The mass was lobulated, firm, crusted by a purulent exudate. A biopsy specimen was studied; the pathologic diagnosis was nonchromaffin paraganglioma. The patient was returned to her family physician with the advice to have further radiation therapy. She has not been examined since.

Case 3. A 62-year-old white man was first examined here in April, 1950, because of poor physical balance of two years' duration. This difficulty was first noted when, after walking up a grade, he suddenly "blacked out" and remained unconscious for several moments. Since that episode his balance was poor, he walked as though he were drunk, and he sometimes staggered or fell to the left. Coughing or sneezing occasionally precipitated such episodes. In addition, he had a roaring sensation in the left ear, and soreness gradually developed in the left temporoparietal area. For a period of about four months he had episodes of vague soreness in the shoulders and weakness in both arms; these lasted about 30 minutes and occurred weekly. Two weeks prior to examination here the soreness became worse; he noticed weakness of the left side of the mouth, difficulty in closing the left eyelid, some dysphasia, and difficult articulation; there was considerable deafness of the left ear since the onset.

Thirty years previously he had sustained an injury to the head. A review of the systems revealed some recurrent episodes of epigastric distress which apparently were well controlled by diet. A renal calculus had been removed in 1945 and more recently the patient had nocturia.

At physical examination the blood pressure was 160/94 mm. of Hg. The left palpebral fissure appeared widened and showed weakness on closing. The tympanic membranes were normal. Palpation of the abdomen disclosed a firm smooth mass on the right side. Neurologic examination revealed nystagmus, bilateral weakness of the left eyelid and the mouth, marked diminution in hearing in the left ear, and tinnitus described as "a puffing train." The Romberg's sign was present, and deviation of the gait to the left was noted. There were no other significant physical or neurologic findings.

Roentgen studies showed evidence of erosion of the superior portion of the left petrous ridge and the region of the external auditory canal. An encephalogram and arteriograms were reported as showing normal findings.

A left suboccipital craniotomy was performed. From the lateral wall of the temporal bone just above the porus acusticus internus a cherry-sized nodule of soft, cystic, reddish tissue protruded externally to the dura and above the jugular bulb. The mass pulsated with heartbeats. A biopsy specimen was obtained and confirmed the clinical impression. Brisk hemorrhage ensued, which was controlled with difficulty. As it was impossible to remove the tumor, the vestibular portion of the eighth nerve was sectioned and the procedure was terminated.

The patient made a good postoperative recovery. Since the neoplasm could not be completely removed, a course of radiation therapy was given: 2,000 r in air was given to each of three portals. The left facial weakness remained, but the staggering gait was greatly decreased. The tenderness in the shoulders and the transient dizziness persisted.

In February, 1951, a tarsorrhaphy was performed on the left eyelid. Some return of function of the seventh cranial nerve was noted, particularly of the left frontal and superorbital muscles. The patient continued to improve until January, 1953. Examination at that time disclosed in the scalp above the left ear a swelling that pulsated synchronously with heartbeats. The seventh cranial nerve palsy was then complete, but no other new neurologic findings were noted. A roentgenogram of the skull showed evidence of further destruction of the squamous and the petrous portions of the left temporal bone. For the first time the left tympanic membrane bulged and the landmarks were lost. Further radiation therapy was given at another hospital, and when last seen in March, 1954, there was further enlargement of the mass above the left ear.

Case 4. A 34-year-old white woman was first examined here in July, 1951, because of loss of hearing in the left ear of approximately four years' duration. In December, 1950, she was examined by a physician who discovered a mass in the left auditory canal; part of the mass was excised. There was no improvement in her hearing.

Examination here disclosed a large, polypoid, pedunculated, epithelial-covered mass in the left external auditory canal. There was a notable conduction type of deafness of the middle ear. An aural polypectomy was performed, but the lesion could not be entirely removed. One month later a radical mastoidectomy was performed; neoplasm filled the entire middle ear and extended through the aditus into the antrum. Apparently complete removal was possible. Microscopic sections of this tissue showed it to be identical to that of the lesion removed from the external auditory canal; a diagnosis of nonchromaffin paraganglioma was made.

There was no recurrence of the lesion for one year after radical removal, but, upon examination nearly four years postoperatively, in April, 1955, there was a suggestion of recurrence as a small zone of reddish discoloration in the operative site. A biopsy specimen of this material in February, 1958, was diagnosed as recurrent neoplasm.

Case 5. A 49-year-old white woman was first examined here in March, 1952, because of tinnitus of four years' duration of the right ear. Previously she had consulted her family physician who diagnosed the condition as chronic tonsillitis; she underwent a tonsillectomy and was unimproved. In April, 1951, she experienced some loss of hearing and a right aural polyp was discovered. A polypectomy was performed and complete loss of hearing in that ear ensued. In October, 1951, a transient right facial

weakness developed and lasted for two weeks. At the same time there was some pain in the right eye, which persisted and was present at the time of her examination here. In March, 1952, the facial weakness again returned, and with it the inability to close the right eye. Headaches, diplopia, or equilibratory disturbances were absent.

Physical examination here disclosed a complete loss of hearing in the right ear. No caloric response could be elicited. The right tympanic membrane was largely replaced by scar tissue. Neurologic examination disclosed hypesthesia of the right trigeminal nerve in all divisions. Palsies of the seventh through the twelfth cranial nerves with right lingual atrophy were noted. A roentgenogram of the skull showed evidence of only some clouding of the mastoid air cells on the right, interpreted as a chronic mastoiditis.

A right suboccipital craniotomy was performed in June, 1952. A neoplastic mass lay along the floor of the posterior fossa. A frozen section of a biopsy specimen was reported as a nonchromaffin paraganglioma. The neoplasm could not be excised and the operative procedure was terminated. The patient remained unconscious until the fourteenth postoperative day when, despite supportive measures, death occurred from bronchopneumonia.

Necropsy findings. At necropsy, extensive involvement of the right temporal bone was present. Protruding from the internal auditory meatus was a polypoid, firm, reddish, slightly granular mass that was 1 cm. in diameter *(Fig. 1)*. Beneath the mass was a

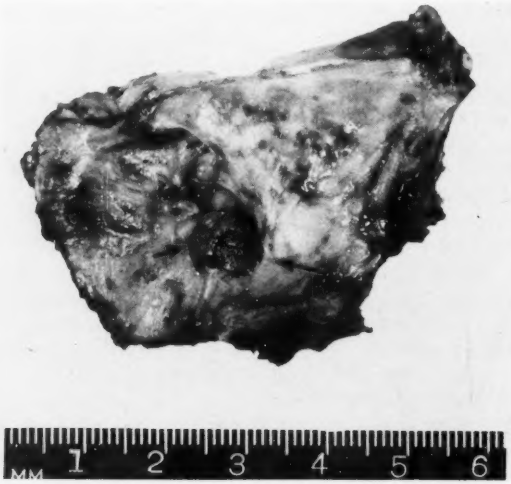

Fig. 1. Case 5. Photograph of the petrous portion of the temporal bone showing mass of neoplastic tissue protruding through the internal auditory canal.

large conglomeration of soft gray-yellow tissue that partially displaced and had destroyed the petrous portion of the temporal bone and the medial portion of the mastoid process, almost at the level of the styloid process *(Fig. 2)*. A tongue of tissue extended anteriorally and extradurally to the region of the pituitary fossa, but did not encroach

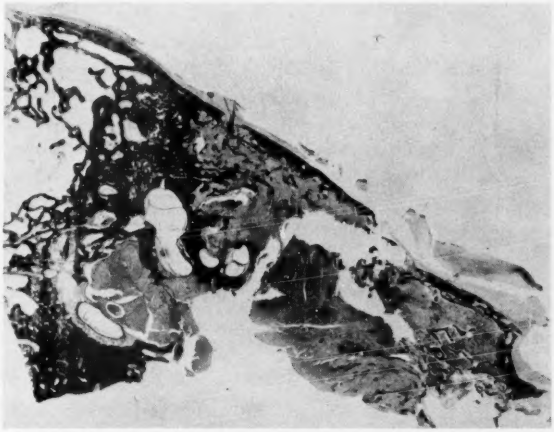

Fig. 2. Case 5. Photomicrograph of a celloidin mount of the coronal section of the petrous portion of the temporal bone showing neoplastic invasion of the petrous ridge and the mastoid air cells.

upon it. Caudally, at the exit of the jugular foramen, the tumor surrounded the jugular bulb and the jugular vein for a distance of 1.0 cm.

Sections of the neoplasm removed for biopsy, and at necropsy, showed the tumor to be comprised of small-sized polyhedral and spindle cells with hyperchromatic oval to elongated nuclei and granular acidophilic cytoplasm *(Fig. 3)*. The cell margins often were indistinct. In some areas the neoplastic cells were arranged in cords and ill-defined masses; in other areas an alveolar arrangement was comprised of well-defined cell nests. Numerous capillary-sized endothelial-lined spaces were present, and were separated from the conglomerations of neoplastic cells by delicate bands of connective tissue (reticulum) *(Fig. 4)*. Rather broad septa of hyalinized connective tissue traversed the tumor, often isolating nodular areas of the neoplasm. Mitotic figures were not seen. Zones of necrosis and rare zones of calcification were present.

Case 6. A 56-year-old white man was first examined here in October, 1953. He had been in apparently good health until three months before, when he noticed gradual loss of vision in the left eye, drooping of the left eyelid, and increasing headache. Shortly after the onset he became dizzy and acquired a staggering gait; early in October he noted difficulty in swallowing, also slurring of speech.

Physical examination disclosed a dilated, fixed, left pupil, absence of left corneal reflex, and presence of palsy of the left oculomotor nerve. There was hypalgesia of the left fifth cranial nerve, weakness of the facial nerve, decreased hearing bilaterally, and an inability to swallow. Babinsky's, Gordon's, and Hoffmann's signs were present bilaterally, and the abdominal reflexes were absent bilaterally. Romberg's sign was present as evidenced by a gait that was notably ataxic. The spinal fluid pressure was 110 mm. of water. Analysis of the fluid showed: a faint trace of globulin, a negative serologic test, and a normal colloidal gold curve. Roentgen examination of the skull

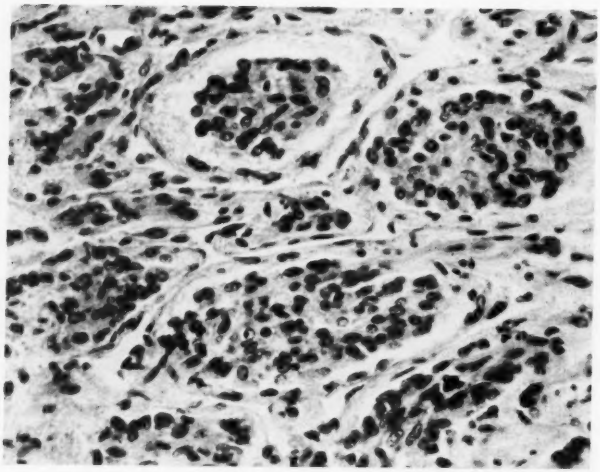

Fig. 3. Case 5. Photomicrograph of neoplasm showing the well-defined nests of the glomic cells separated by abundant vascular network. Hematoxylin-eosin—methylene blue stain; magnification X 250.

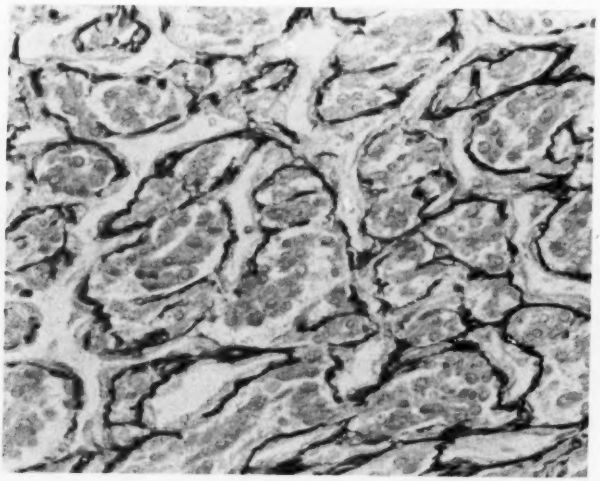

Fig. 4. Case 5. Photomicrograph of neoplasm showing argyrophilia of capillary basement membranes. The cellular aggregates are not a part of the vascular channels. Wilder's reticulin stain; magnification X 250.

disclosed evidence of widening of the left internal auditory canal, of destruction of bone along the left petrous ridge, and of erosion of the dorsum sellae.

On October 30, 1953, a right suboccipital craniotomy was performed. When the pontine cistern was entered, a lobular, vascular mass the size of a small cherry was disclosed above and anterior to the auditory nerve well forward of the petrous apex. The surrounding dura was extremely vascular, as was the tumor. The mass appeared to arise from the apex of the petrous bone approximately at the point where the trigeminal nerve should have crossed, but the nerve itself was nowhere in evidence. The patient failed to rally from the operative procedure and died on the ninth postoperative day.

Necropsy findings. At necropsy, a cherry-sized polypoid mass was seen at the apex of the petrous ridge along with destruction of the medial 2 cm. of the structure. The tumor surrounded the fifth cranial nerve at that site, and extended laterally into the mastoid air cells. There were no other significant gross findings. Microscopically the specimens of tissue removed at operation and at necropsy showed identical histologic structures. The neoplasm was formed by cells that were somewhat spindly, or sharply curved. The nuclei were vesicular, hyperchromatic, and somewhat irregular in outline. The cytoplasm was scanty, granular, and acidophilic. Mitosis was prevalent. The neoplastic cells were arranged principally in solid masses that were traversed by numerous endothelial-lined vascular channels, usually of capillary size but occasionally one was larger. Reticulum stains outlined numerous small-sized vascular channels, and revealed delicate reticulum fibers extending into the neoplasm from the vascular channels. The neoplastic cells were closely related to the vascular channels but were separate from them.

Clinical Features

Nonchromaffin paragangliomas occur in women three times as often as in men. The age of onset in both sexes ranged from 17 years to 85 years, with an average age of approximately 47 years. In general, the duration of symptoms before diagnosis is long, averaging about seven years, within a range of about six months[33, 34] to more than 20 years.[35-40] One hundred and ninety published cases[1,2,5,6,8,9,14,15, 33-101] with abstracts of 165 of these cases are available to us. These and our own six cases are the basis of an assessment of the clinical features. The symptoms and findings associated with these neoplasms are variable, but may be classified into three groups: (1) principally otic, (2) otic and neurologic, and (3) (the smallest group) primarily neurologic. In a slightly different fashion, Bickerstaff and Howell[68] classified 90 reviewed cases into four groups based on the order of appearance of symptoms; i. e., Group I (49 cases), aural symptoms only; Group II (20 cases), neurologic symptoms developing many years after aural involvement; Group III (17 cases), neurologic and aural symptoms developing concurrently; and Group IV (4 cases), neurologic involvement before aural symptoms.

The clinical features most commonly noted are the presence of an aural polyp, loss of hearing, otorrhea, facial nerve palsy, and pain. The lesions affect the right side about as often as the left: in 145 cases the side that was affected was recorded,

and the right side was involved 69 times, the left 76. In most instances, tinnitus was an associated symptom, variably described as roaring, blowing, or pulsating, and often synchronous with the pulse rate. Polypoid masses were observed in the external auditory canal in 106 patients, and bluish or reddish discolorations of the tympanic membrane often associated with bulging of the tympanic membrane in other patients. Capps[71] has published excellent colored plates of the appearance of the tympanic membrane at various stages of the disease. In a few patients, spontaneous bleeding occurred presumably as a result of ulceration; in all patients in whom biopsy was attempted, some measure of hemorrhage was encountered. A bruit was heard over the mastoid process in a few patients. A discharge, usually similar to that in recurrent otitis media, or of a watery character, was observed in 63 patients. Pain in the ear was noted in 33 patients and was usually referred to the involved ear. In two of these the pain was somewhat similar to that recorded for tic douloureux.[33, 37] Pain, however, more often occurred late in the disease and generally was dull in character. Several patients remarked that their ears felt "stuffed up." Roentgen findings have been described in almost all cases. These usually include evidence of erosion of the petrous portion of the temporal bone, sclerosis of the mastoid air cells, and enlargement of the jugular foramen.[65,74,95]

Approximately 50 per cent of the cases analyzed reported neurologic signs and symptoms usually in the form of cranial nerve palsies. Henson, Crawford, and Cavanagh[48] reported an incidence of 40 per cent in the 77 cases they analyzed, and Bickerstaff and Howell[68] found 65 per cent cranial nerve palsies in their 90 cases. In most of the patients the neurologic symptoms developed after the aural signs and symptoms. The cranial nerves involved were usually the seventh through the twelfth on the affected side, though the fifth and sixth nerves occasionally were involved; of 171 patients, 17 had involvement of the fifth nerve, 15 of the sixth nerve. Figi and Weisman[98] describe one patient whose third through the twelfth cranial nerves were affected. In the collected cases, the facial nerve was involved 65 times, the glossopharyngeal nerve 40 times, the vagus 40 times, the spinal accessory nerve 29 times, and the hypoglossal nerve 36 times. These statistics are not in agreement with those of Henson, Crawford, and Cavanagh[48] who reported a considerably higher incidence of involvement of the ninth through the twelfth cranial nerves. However, a good proportion of the patients considered were seen during the aural aspect of the disease, and perhaps were prevented from having further immediate progression of the disease. Siekert[97] catalogued the neurologic abnormalities in 33 patients with paragangliomas of the glomus jugulare. He found that the facial nerve was involved in 27 patients, and other neurologic defects were present in 14.

Henson, Crawford, and Cavanagh[48] state that the earliest neurologic symptoms are dryness and stiffness of the tongue, a sense of pharyngeal irritation, dysphasia, and aphonia. Such symptoms were observed in part in one of our patients (case 1). They also point out that the hypoglossal nerve often is involved before the

ninth, tenth, and eleventh cranial nerves are. Nystagmus has been described frequently and may be vertical, horizontal, or even rotatory as in our case 5. Ataxia has been a frequent symptom and was present in three of our patients. In one patient (case 3) it was completely alleviated by sectioning the vestibular portion of the eighth cranial nerve.

Less common and unusual symptoms may be observed. In one patient (case 6) the presenting complaint was gradual loss of vision in the left eye and drooping of the left eyelid. Episodes of dizziness and syncope were presenting complaints (case 3), precipitated by coughing, sneezing, hyperventilation and physical exertion. Huppler, McBean, and Parkhill[6] described a patient with similar difficulties and, as for our patient, relief was obtained by radiation therapy. Pyramidal tract signs have also been observed, though they are uncommon.[33, 37,48,54] Papilledema is an extremely rare phenomenon, and was noted in three cases.[42,85,96] In Zacks'[9] second case the papilledema was associated with personality changes and dysphagia. Hemianopsia has been reported but rarely.[91]

Although this disease may have protean manifestations, a history of increasing deafness, chronic recurrent discharge from the external auditory canal, the appearance of cranial nerve palsy, and the presence of a polypoid mass in the auditory canal and protruding through the tympanic membrane should arouse a high index of suspicion for the diagnosis of a neoplasm of the glomus jugulare.

Of interest is the observation that neoplasms of the glomus jugulare may show a familial tendency. According to Winship and Louzan,[50] Bartels published an exhaustive study of the disease entity and described not only a familial tendency but a multicentricity of lesions occurring in members of the same family. Seven persons of one family, including three generations, had neoplasms of the glomus jugulare, of the carotid body, or of both structures. Three sisters had tumors of the glomus jugulare, and died as the result of the disease;[47] and other reports of familial occurrence have been published.[50]

Pathologic Features

Grossly, the tumors of the glomus jugulare vary; often they are polypoid and fill the entire middle ear. Characteristically, they slowly expand and, depending upon their origin, they may extend outward into the external auditory canal, or may grow through the petrous pyramid or the internal auditory canal. After extension into the cranial vault, they most often grow extradurally (cases 1, 5, and 6), but may extend through the dura.[34,46,48,57,73,94,95] The tumors may grow forward toward the clinoid processes or posteriorly into the posterior fossa (cases 1, 3, and 5). In one patient the jugular foramen was completely closed by the tumor,[48] and in another patient the tumor arose in the jugular foramen.[62] Contiguous structures are obviously encroached upon and symptoms vary according to the fortuitous location of the expanding neoplasm. Within the middle ear itself the destruction of adjacent bone easily permits extension into the mastoid; one

tumor extended into the nasopharynx.[55]

Grossly, the cross sections of the neoplasms are variable. One tumor was described as grayish-brown and spongy with a few calcareous deposits;[33] another was grayish-white, smooth and polypoid;[55] in two of our patients the tumors were smooth, firm, and grayish-pink. Most of the descriptions emphasize the marked similarity to granulation tissue.

The microscopic appearance of these neoplasms is pathognomonic. There is a high degree of vascularity. The blood vessels are thin-walled, of capillary size, composed of a single layer of endothelium, and supported by delicate reticulum. Conglomerate masses of "epithelioid cells" are arranged in close proximity to the blood vessels and thus form an alveolar arrangement in some areas. These cells are polygonal or round, with pale-staining acidophilic cytoplasm that usually contains fine acidophilic granules. The cell boundaries often are indistinct, as exemplified in our case 3. Phosphotungstic acid-hematoxylin stain reveals a small amount of collagen between the individual nests of neoplastic cells. Lattes and Waltner[5] pointed out that silver stains for reticulin show an argentophilic framework composed of delicate reticulin fibers that branch from the subendothelial membranes of the vessels and surround nests of neoplastic cells. In only one of our cases (case 6) was mitosis prevalent; this is an uncommon finding. The chromaffin reaction has been reported as negative by those who have done it.[5,42,56] Lattes and Waltner[5] found a few axons between tumor cells. Zak[42] reported negative reactions of the neoplasm in regard to alkalin phosphatase and acid phosphatase, and to lipase. Zacks[9] found cholinesterase, phospholipids, and small amounts of neutral fat in the neoplastic cells but no glycogen.

Malignancy is a rare feature of these neoplasms, but though they are regarded as benign, anatomically they are potentially lethal. A few well-documented cases of malignancy have been reported;[5,47,48,56,74,76] metastasis occurred to the jugular lymph nodes, liver, lung, and bone, and the lesions were identical with those of the primary tumor in the middle ear.

Multicentric involvement of the various nonchromaffin paranganglia has been reported.[5,9,15,49,61,100] Kipkie,[49] it is believed, reported the first instance of a tumor of the glomus jugulare occurring in conjunction with a carotid body tumor on the contralateral side; Lattes and Waltner[5] reported a similar case, and Zacks[9] recently reported a case of nonchromaffin paragangliomas involving the carotid body, glomus jugulare, and retroperitoneum. Lattes[15] reported two cases of multicentric lesions of the chemoreceptor system, neither of which involved the glomus jugulare. McNeill and Milner[93] treated a patient who had bilateral neoplasms of the glomus jugulare; the type of neoplasm of the right ear was not histologically confirmed. Zak[42] considers Von Hippel-Lindau's disease as an example of multicentric neoplasia, and evolved a new concept that glomic tissue is the origin for cerebellar angioblastoma, Von Hippel-Lindau's disease, and related supertentorial neoplasms.

Prognosis and Treatment

In reviewing the cases, we have a distinct impression that many patients are apparently free of gross evidence of disease for variable periods of a few months to several years. There are many instances in which the course of the disease extends over a period of many years.[5,36-40,47,57,77,89,92] In one patient there was no evidence of recurrence 17 years after radical mastoidectomy and radium implantation.[47] However, the disease is a slowly progressive one as indicated in our patients by the average duration of symptoms, which is 7.4 years after operation. For the most part, follow-up information is too recent postoperatively to allow accurate prognostication at this time. Perhaps the reason that the prognosis in regard to these lesions is so poor is because symptoms arise from the slow, expansile growths and, when the symptoms are of sufficient severity that the patient seeks medical aid, the tumor has already enmeshed itself within the architectural intricacies of the temporal bone, making removal difficult if not impossible.

The treatment of these neoplasms, expressed in general terms, has been surgical, radiative, either with roentgen ray or radium; some have been merely followed. Whenever possible, surgical removal of the tumor has been attempted, and has met with some measure of success when the lesion was largely confined to the middle ear.[5,35,38,44,47,76,99] Radical mastoidectomy has been most frequently employed. Shambaugh[99] has described a technic for hypotympanotomy when the lesion is limited to the hypotympanum and the tympanic cavity. In a number of instances this operation has been combined with a course of radiation therapy. Many patients have gone two years or more without recurrence.[5,34,39,44,47,64,95] Radiation alone has been employed less frequently and with some measure of success.[5,34,39,47] Stewart, Ogilvie, and Sammon[92] believe that irradiation causes endothelial proliferation within the vessels of the tumor, and that the resulting decrease in vascularity reduces the size of the tumor. They doubt that there is any marked effect on the neoplastic cells per se. Alexander, Beamer, and Williams[37] treated a patient with 2,080 r in air through each of two occipital portals, and six weeks later administered an additional 9,000 r through a right occipital portal. Two years later the patient was significantly improved. Angiograms taken after the first course of roentgen therapy and again eight months later showed less vascularity of the tumor. Riemenschneider, and associates[65] expressed pessimism concerning the value of radiation therapy for this disease. When neurosurgical procedures have been necessary the mortality has been high. In only one patient was the entire intercranial neoplasm successfully removed.[37]

Our own experience parallels much of that mentioned. Two patients (cases 1 and 3) were treated essentially by roentgen therapy after the suboccipital craniotomies had accomplished little more than providing histologic proof of the type of tumor. In the one patient (case 3) a division of the vestibular portion of the eighth cranial nerve was beneficial. There has been no progression of the disease for eight years in one patient (case 1), though she still has residual tumor. Case

3 illustrates the slow, relentless progression of the neoplasm for four years after roentgen therapy.

In one patient (case 4) only, a radical mastoidectomy was performed. Five years after surgery a small reddish discoloration developed in the mastoid cavity; it slowly grew larger, and in February, 1958, it was removed and was found to be a recurrence.

In general, the prognosis must be considered guarded, but there is the optimistic note that with early diagnosis treatment may be helpful. When surgical removal is possible this would seem to be best, particularly when the lesion appears to be confined to the middle ear and to the adjacent mastoid. Irradiation therapy is of some value when surgical removal cannot be complete. Occasionally neurosurgical procedures may be necessary.

One additional therapeutic note is worthy of mention. Ligation of the external carotid artery and jugular vein may relieve the bruit.[33,36] Ligation of the external carotid artery alone has been beneficial;[40,95] in one patient the common carotid was ligated but death ensued because of cerebral infarction.[40]

In a series of 167 cases (161 previously published[5,9,33,38,42,46,48,56,61,62,68,71-76,89,91,92,95,99] and our six), 32 patients died, including two of our patients (cases 5 and 6). Eleven of the patients died postoperatively after craniotomy, and three after procedures in the mastoid and the middle ear. The deaths were due to postoperative surgical complications. In no patient was it possible to remove all of the neoplasm, and in all patients the marked vascularity of the tumor was a severe obstacle, and in almost all, intracranial extension was present. Nineteen patients survived the postoperative period but died later, 13 patients from causes directly concerned with the neoplasm itself.

The 32 deaths offer only an indication of the role of these neoplasms in causing fatality. The intracranial extension of the tumor would appear to be the major cause of death. Neurosurgical postoperative mortality is high, probably because of the extremely difficult technical problems encountered, involving both the great vascularity of the neoplasm and the anatomic relationships.

Four patients died apparently as a result of metastatic disease, although metastatic disease was present at the time of death in six patients, secondary deposits of neoplasm were found in the liver, lungs, spleen, and bones. Intracranial extension of the neoplasm accounted for six deaths.[5,33,38,42,61,75] Poppen and Riemenschneider's[33] patient survived four years and eight months after the onset of symptoms; at necropsy a large, friable mass displaced the cerebellum and medulla, filled the middle ear and the mastoid air cells, and extended forward to the posterior clinoid process into the petrous ridge and the pharynx. Zak's[42] second patient died of respiratory distress secondary to displacement and deformity of the pons and the medulla by the neoplasm, which had grown through the jugular foramen. Three other patients died of the effects of the disease, although the exact mechanisms causing death could not be determined.[92,93,100] Cerebral

abscess, secondary to middle ear disease, accounted for two deaths.[42,97] Six patients with the disease died, but of other causes, such as cerebral hemorrhage, cerebral infarct, and bronchopneumonia.[9,18,22,38,40,68]

Summary and Conclusions

Six cases of nonchromaffin paraganglioma of the glomus jugulare are presented. In two patients (case 2 and 4) the signs and symptoms of the disease were aural only. The presence of an aural polyp, marked loss of hearing, and tinnitus were the principal clinical features. In one patient (case 4), even though complete removal appeared to be possible, recurrent neoplasm developed after several years. The neural aspects of the disorder are exemplified in the other four cases; two of the patients died and necropsy was performed. Cranial nerve palsies involving the fifth through the twelfth cranial nerves occurred in three patients (cases 1, 5, and 6). One patient (case 6) in addition had a third cranial nerve palsy. The necropsy findings in cases 5 and 6 illustrate the extensive destruction of the petrous portion of the temporal bone, the extradural extension of the neoplasms, and the encroachment upon vital structures of the posterior fossa.

One hundred and ninety cases in the literature are available to us, and of this group, 165 case abstracts have been examined in addition to those of our own six cases.

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AMMONIA INTOXICATION FROM BANK BLOOD IN PATIENTS WITH CIRRHOSIS OF THE LIVER

A Clinical Note

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STUDIES[1-3] of ammonia intoxication in patients with cirrhosis of the liver have shown that the administration of drugs such as chlorothiazide,* acetazolamide,† and ammonium chloride, which have been used commonly in patients with ascites, may cause ammonia intoxication or may increase its severity if it exists. The increased ammonia content of stored blood has been reported,[4-7] and in most clinical conditions is harmless. However, in the cirrhotic patient with hemorrhage that requires massive transfusion, the use of stored blood may precipitate coma because of its high ammonia concentration.

This study was undertaken to determine the rate of increase in ammonia nitrogen in stored blood for the purpose of predicting the ammonia content of blood administered in emergency situations, and for considering means of compensating for this difficulty.

Forty-two samples of whole blood, collected in 500-ml. containers‡ were stored at from 4 to 10° C. as long as 31 days. Analyses for ammonia nitrogen were made through the courtesy of W. R. Faulkner, Ph.D., of the Department of Clinical Pathology, whose modifications of the Conway technic were employed.

There was an average linear increase of 20 μg. per 100 ml. per day in the amount of ammonia nitrogen in stored blood *(Fig. 1)*. In an attempt to explain the unusual values obtained for particular samples, the ease and rapidity of bleeding the donor were evaluated. Easy, rapid bleeding was associated with low values for ammonia; whereas, difficulties with venipuncture and stasis below a tourniquet were correlated with higher values.

Comment

Theoretically, if a patient (weighing 70 kg.) with cirrhosis and bleeding varices had lost 20 per cent of the blood volume, and he was transfused rapidly with 10 units of blood stored for 10 days, the ammonia concentration in the peripheral blood would be increased approximately 100 μg. per 100 ml. Although rarely would blood be administered rapidly enough to produce such a calculated increase, this increment added to that formed in increasing amounts in the gastrointestinal tract might be critical in producing ammonia intoxication and deepening coma.

This complication of transfusion can be controlled at present by three methods.

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* *Diuril (chlorothiazide), Merck Sharp & Dohme.*

† *Diamox (acetazolamide), Lederle Laboratories.*

‡ *Silicone-coated, nonvacuum containers with A-C-D solution, manufactured by Abbott Laboratories.*

The first is that of using only fresh blood, if adequate amounts are available. The second method is an ingenious adaptation of the cation-exchange resin principle as reported by Schechter, Nealon, and Gibbon.[8, 9] These authors used a resin exchange column through which blood from the donor bottle passed before it was administered to the patient. Effective extraction of ammonia and potassium from stored blood occurred at rates of drip as fast as 50 ml. per minute. Unavailability of the necessary equipment is at present a deterrent to the use of this method. A practical, clinical objection is that sodium is the cation exchanged for ammonia and potassium. Sodium thus released and given to the patient may precipitate or increase ascites.

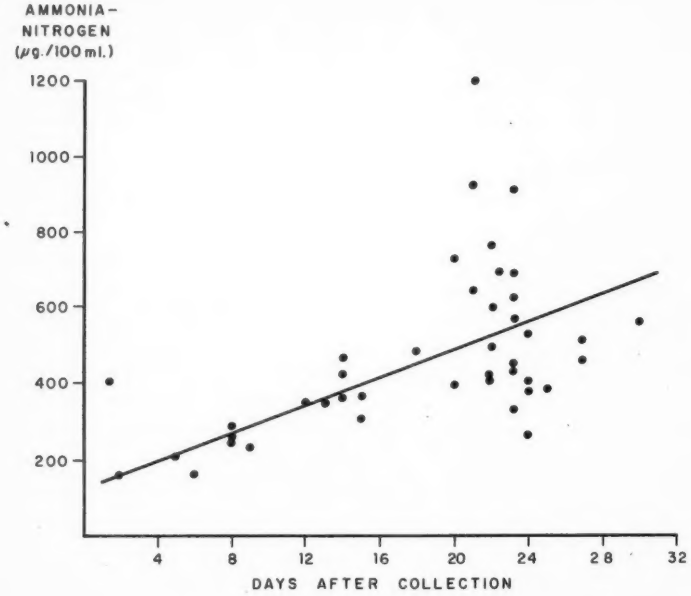

Fig. 1. Graph showing increase of concentration of ammonia-nitrogen in stored blood.

The third and most practical method of controlling the effect of ammonia in stored blood is the simultaneous administration intravenously of arginine.[10] Arginine combines with ammonia in the liver to form urea; this reaction occurs rapidly and continues even in terminal hepatic disease. Arginine monohydrochloride may be simply prepared by adding 25 gm. of analytically pure arginine monohydrochloride to 400 ml. of distilled pyrogen-free water, adding 240 mg. of potassium metabisulfite as an antifungal preservative, autoclaving the solution for 15 minutes at 20 pounds of pressure, and storing it at room temperature. One hundred milli-

liters of 50 per cent dextrose solution may be added prior to use to provide additional calories. Arginine is also available commercially as L-arginine L-glutamate.*

Arginine injected intravenously has been nontoxic in amounts up to 200 gm. per day. Twenty-five grams given every four hours during massive transfusion is sufficient to prevent any potential toxicity due to increased ammonia content of stored blood.

Summary

Ammonia in stored blood increases at an average rate of 20 μg. per 100 ml. per day. Three clinical methods are useful for reducing or controlling ammonia intoxication that may result from massive transfusion in a cirrhotic patient. The most practical method at present is to administer intravenously arginine monohydrochloride simultaneously with the blood as described.

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* *Modumate (L-arginine L-glutamate), Abbott Laboratories.*

VAN NECK'S DISEASE—FACT OR FICTION?

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VAN Neck[1] in 1924 described two children who had swelling and demineralization of the ischiopubic synchondrosis with local pain and soft-tissue reaction. Since then, the term "Van Neck's disease" ("ischiopubic osteochondrosis") has been applied to the roentgen evidence of osseous swelling of the ischiopubic synchondrosis with or without other manifestations. This paper is presented to review the pertinent literature briefly, and to clarify the currently prevalent opinion that the roentgen findings of Van Neck's disease are actually only normal developmental variations.

The development of the pubic bone begins in the fetus during the fifth or the sixth month, when the center of ossification is formed in the horizontal ramus at the edge of the obturator foramen.[2] The ischium normally begins to ossify in the superior ramus in the fetus during the fifth month. As growth progresses, the cartilage between the ischial and the pubic rami is replaced by bone until fusion occurs. This area, called the "ischiopubic synchondrosis," undergoes fusion relatively early in childhood, whereas in the acetabular region, synostosis does not occur until puberty.

Köhler[2] believes that ischiopubic osteochondrosis is observed chiefly in children from nine years to 12 years of age. He attributes the vesicular appearance to a developmental disturbance at the site of fusion.

Both of Van Neck's[1] patients had pain and regional signs of inflammation. The histologic diagnosis based on the findings in the biopsy specimen of bone was osteochondritis. In both cases incision and drainage gave prompt relief of symptoms with somewhat slower regression of the osseous change.

In 1933, Heeren[3] reported that of 100 asymptomatic children whom he examined, 16 had the roentgen findings described by Van Neck. More recently, Junge and Heuck[4] studied the roentgen findings in 358 asymptomatic children ranging in age from five to 15 years. Approximately one seventh of the children had distention or thickening of the ischiopubic synchondrosis. They[4] concluded that muscular insertions in the area produce a stress reaction in the bone, and that inflammation had no part in producing the roentgen findings.

A complete survey was published by Caffey and Ross[5] in 1956. Roentgenograms of 549 children between the ages of two years and 12 years were studied. The roentgenograms were selected on the basis of a review of the clinical histories of the children; none were included of any child who had a systemic disease that

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could have affected osseous development, or any regional signs or symptoms of a disease process. Each patient's roentgenograms were examined to determine the time at which fusion had occurred, and whether there was evidence of swelling or uneven mineralization. More than 50 per cent of the children from six years to 10 years of age had evidence of unilateral or bilateral swelling and uneven mineralization. Of the 549 children, 246 (45 per cent) at some time had evidence of osseous swelling of the ischiopubic synchondrosis.

Caffey and Ross[5] concluded that fusion of the ischial and pubic rami occurred at varying times in children between the ages of four years and 12 years; in many children fusion was preceded by osseous swelling that sometimes persisted for several years. They believed that the high incidence of the osseous swelling in healthy children suggested that Van Neck's disease is rare, and that many of the examples published are variations in normal growth. Our experience confirms their conclusion.

Material and Method

In order to visualize the normal process of osseous growth and fusion of the ischiopubic synchondrosis, serial roentgenograms were selected from films taken at the Cleveland Clinic during the months of June, July, and August, 1958. These roentgenograms *(Figs. 1 through 8)* trace the development of the ischiopubic synchondrosis in children from the age of five days to three years, when fusion is complete. The clinical history of each patient was analyzed to exclude those histories in which symptoms could be attributed to a disease entity or pathologic process involving the ischiopubic synchondrosis or contiguous areas.

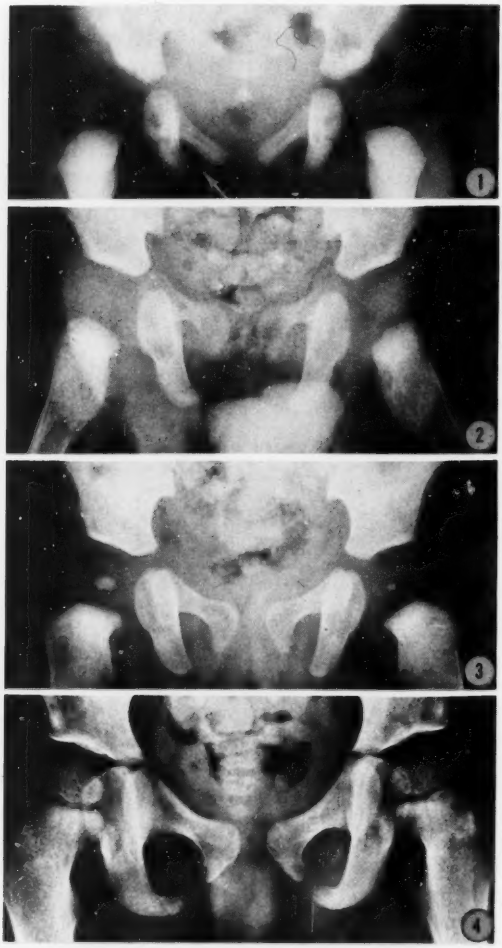
Figures 9 through *16* were among the roentgenograms obtained during the routine examination of 86 children, none of whom had any signs or symptoms referable to Van Neck's disease. The diagnosis at the time of roentgen examination is presented in each legend.

Summary

Since Van Neck's published paper in 1924, the term "Van Neck's disease" has been applied to any ischiopubic synchondrosis that roentgenographically is observed to be swollen or demineralized. Although both of Van Neck's patients had localized inflammation, the diagnosis of Van Neck's disease is made today on the basis of the roentgen findings in children who are free of regional inflammatory signs, and sometimes even in those who are free of regional symptoms.

Several detailed studies have been made and the incidence of Van Neck's roentgen findings is so high in asymptomatic children that the current opinion is that the roentgen findings of Van Neck's disease are normal variations in the development of the ischiopubic synchondrosis.

Roentgenograms illustrating the usual fusion process of ischiopubic synchondrosis



Figures 1 through 8 demonstrate the gradual fusion as it occurs in children from the ages of five days to three and one-half years. **Fig. 1.** Five days. (Infant girl examined because of problem in feeding; diagnosis undetermined.) **Fig. 2.** Three months. (Infant boy; diagnosis, cerebral atrophy.) **Fig. 3.** Six months. (Infant girl; diagnosis, ovarian agenesis.)

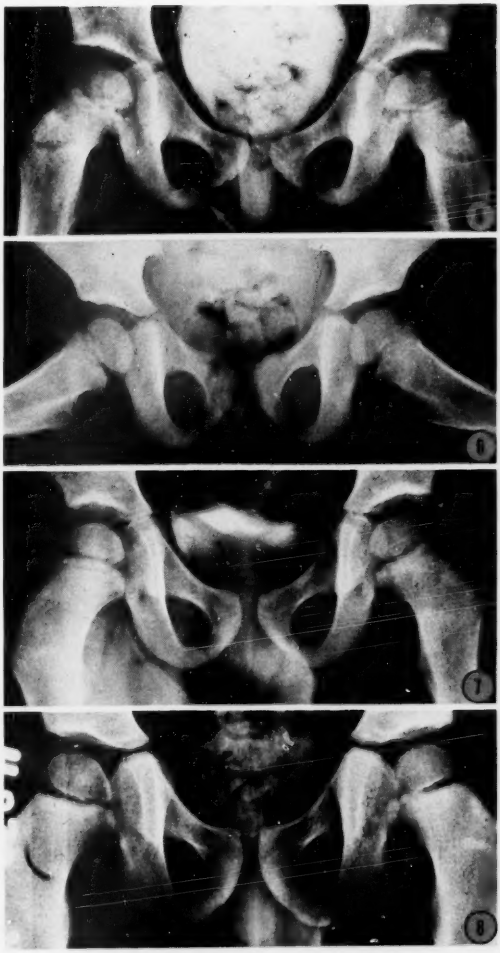
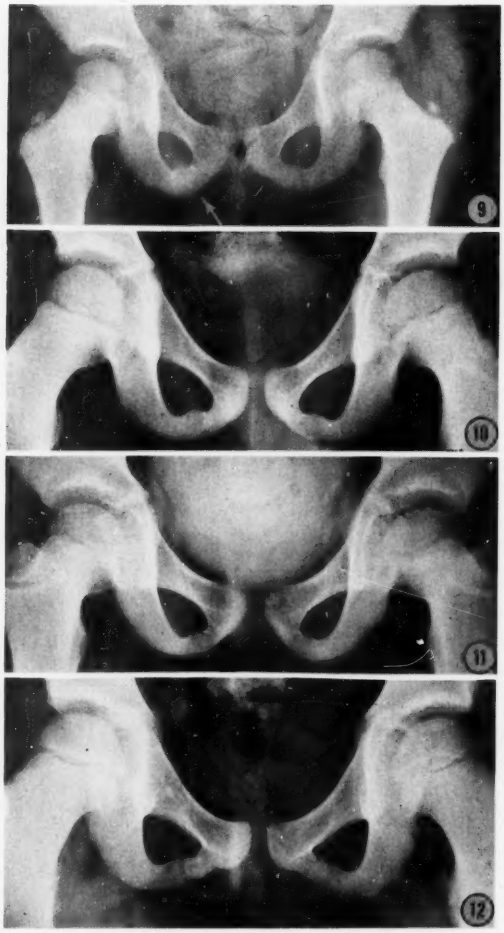


Fig. 4. Twenty-four months. (Girl; diagnosis, pigmented nevus on the back.) **Fig. 5.** Forty months. (Girl; diagnosis, tubercular node in the neck, but no abnormal roentgen findings. **Fig. 6.** Thirty months. (Girl; diagnosis, retinoblastoma.) **Fig. 7.** Thirty-six months. (Boy; diagnosis, nephrosis.) **Fig. 8.** Thirty-six months. (Boy; diagnosis, postpolio weakness.)

Roentgenograms illustrating normal variations of the usual fusion process of ischiopubic synchondrosis



Figures 9 through 16 demonstrate the so-called "swelling" and "cystic changes" in patients from five years to 15 years of age with no signs or symptoms referable to those areas. Note that in some there is evidence that the process is unilateral. **Fig. 9.** Five years. (Boy; diagnosis, mental retardation.) **Fig. 10.** Six years. (Boy; diagnosis, nephrosis.) **Fig. 11.** Six and one-half years. (Girl; diagnosis, urethritis.)

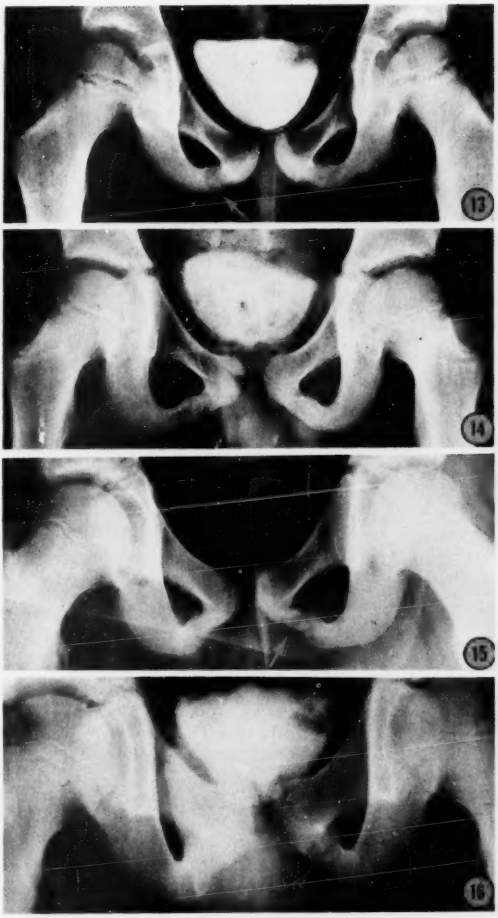


Fig. 12. Seven years. (Girl; diagnosis, pharyngitis.) **Fig. 13.** Seven years. (Boy; diagnosis, staphylococcal enteritis.) **Fig. 14.** Eight years. (Boy; diagnosis, chronic cystitis.) **Fig. 15.** Thirteen years. (Boy; diagnosis, sickle-cell trait.) **Fig. 16.** Fifteen years. (Boy; diagnosis, urinary frequency.)

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ARGININE MONOHYDROCHLORIDE—A SOURCE OF CHLORIDE IN THE TREATMENT OF HYPOCHLOREMIC STATES

A Clinical Note

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IN certain clinical conditions a metabolic derangement may require rapid correction of severe hypochloremia. The administration of sodium chloride as a source of chloride may necessarily be limited because of the dangers of overloading with sodium, and an adequate amount of ammonium chloride may be contraindicated in cirrhotic patients because of the risk of inducing coma. Massive chloride replacement with potassium chloride and calcium chloride is not possible, particularly in patients who are dehydrated and oliguric, because of the potential toxicity of the associated cation. Hydrochloric acid for intravenous use is not usually kept available and may not be suitable in certain clinical situations.

On the other hand, arginine is available as arginine monohydrochloride; the molecular formula is $C_6H_{14}N_4O_2$ HCl. When prepared as a solution containing 25 gm. of arginine hydrochloride in 500 cc. of distilled water, the chloride content is 119.4 mEq. The tonicity of this solution is approximately 575 m-osM.

The mixture is prepared for clinical use (intravenous) by adding 25 gm. of arginine monohydrochloride to 500 cc. of distilled water, filtering it to remove any particles contaminating the analytically pure commercial reagent, adding to it 0.3 gm. (0.06 per cent) of potassium metabisulfite as a preservative, and autoclaving the solution for 20 minutes at 15 pounds of pressure. The arginine monohydrochloride is stable at room temperature for long periods. In clinical usage it has proved to be nontoxic when given in amounts as rapidly as 25 gm. in 15 minutes and a total amount of 250 gm. in 24 hours.

A typical clinical situation in which arginine monohydrochloride may be useful is that of the cirrhotic patient with ascites, obstructing duodenal ulcer, and a severe hypochloremic hypokalemic alkalosis. In such a patient the use of excessive amounts of sodium chloride is contraindicated because of the ascites, and the use of ammonium chloride in large amounts is contraindicated because of the danger of precipitating ammoniogenic intoxication. However, the intravenous administration of arginine monochydrochloride and potassium chloride corrects the metabolic imbalance rapidly and safely without increasing ascites or inducing intoxication. In a few patients in whom ammonia intoxication existed, such treatment was associated with a dramatic reduction in ammonia in the peripheral blood, and the clearing of coma or stupor coincident with the correction of the hypochloremia. A concomitant transient increase in blood urea may occur as a result of accelerated urea formation in the liver.

ERRATA

In the January, 1959, issue of this journal, on page 18, in Table 2, column 2, the figure 0.1 should read *0.01*, and similarly the lower two figures in column 3 and the lowest figure in column 4 instead of 0.1 should read *0.01*.

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